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Study of So-Called Penicillin-Resistant Gonococcal Infections: During the years from 1946 to 1948, a total of 66 patients - 57 males and 9 females - assumed to be failures of penicillin treatment were studied. Fifty-one were found to be gonococcus-positive by culture and/or smear diagnosis, and 15 were gonococcus-negative. No case was declared gonococcus-negative before 3 bacteriologic examinations, done over a period of about from two to three weeks, yielded negative results.

Among the 51 infected patients, 27 admitted sexual exposure following their previous treatment, 19 denied any additional sexual contact, and 5 patients gave no reliable information.

Of the 27 patients who admitted sexual exposure after their last treatment, 5 were unable to attend for further study.

Consequently, 46 patients with gonococcal infections received re-treatment. A single intramuscular injection of 150,000 units of sodium penicillin in water-in-oil emulsion was given to 9 patients. Seven were cured and two became delinquent following re-treatment. Among this group were three patients who had previously received as many as two and three injections each of 150,000 units of penicillin; one of these had received three injections of 400,000 units each without success.

A single intramuscular injection of 200,000 units of sodium penicillin in water-in-oil emulsion was administered to five patients; all were cured. In this group two had been previously treated with two injections of 150,000 units of penicillin and one patient with four injections of the same dose without apparent success.

A single injection of 300,000 units of sodium penicillin in water-in-oil emulsion was given to 26 patients. Only 15 patients remained for an adequate observation period and all were cured. Among this group were four patients who had failed to respond initially to two and three injections of an identical dose of penicillin.

Each patient in a group of six with initial failure to two injections of penicillin in amounts of from 150,000 to 300,000 units requires a separate discussion. The re-treatment schedules, the number of single injections necessary to achieve cure, and the vehicle in which the drug was administered were in no way uniform. Arbitrarily and for experimental purposes, penicillin in aqueous solution was used in three patients, and for the same reason streptomycin in one patient. Two patients responded to a single injection of penicillin; one to 1,000,000 units of sodium penicillin in aqueous solution only, and one to 500,000 units of the drug in water-in-oil emulsion. Two patients did not respond to re-treatment with a single injection of 300,000 units of penicillin. However, one of them

responded to the second injection of an identical dose given one week later, and the other patient was cured by a single injection of 600,000 units of sodium penicillin in aqueous solution. The other two patients were not affected by two injections of varying amounts of penicillin such as of 200,000 and 300,000 units in one case, and of 300,000 units and 600,000 units in the other; the latter dose was given in aqueous solution. These repeated injections were given at an interval of about from one to two weeks. Cure was finally achieved in one of these patients by a single injection of 500,000 units of penicillin in water-in-oil emulsion, and in the other patient by a single injection of 0.5 Gm. of streptomycin sulfate in aqueous solution.

Patients considered cured had an average observation period of 19.8 days with an average number of 3.8 cultures, taken from the urethra and the prostate or the urethra and the cervix.

In order to obtain more information on the behavior of the individual strain of gonococcus to penicillin and streptomycin, 111 strains of the gonococcus, cultured on Peizer's medium and identified by fermentation tests, were examined. There was a wide range in their sensitivity to each antibiotic agent. This variation of sensitivity of individual strains appeared to be consistent, for, the majority of repeated tests yielded identical results concerning the degree of sensitivity. As it was suggested previously this strain variation is probably one of the factors which necessitates the use of larger amounts of penicillin in some cases in order to achieve cure.

Response to re-treatment with penicillin of 34 patients with gonorrhea indicates that no true penicillin-resistant infection could be found.

Causes for failure of penicillin treatment are evidently either reinfections, or the fact that a few patients require larger amounts of the drug for cure than the majority. Whether or not clinical complications such as walled-off foci of infection not easily accessible to the drug require likewise larger amounts or repeated doses of penicillin in some patients remains to be seen.

Streptomycin may be considered as a therapeutic agent for gonococcal infections, if penicillin should fail. (Am. J. Syph., Gonorr. & Ven. Dis., Jan. '49, A. Cohn et al.)

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Cardiovascular Syphilis: It is reasonably established that the adequate treatment of early syphilis affords partial, if not complete, protection against the development of clinically recognizable cardiovascular syphilis. Kemp and Cochems in 1937 studied 743 patients who had received varying amounts of treatment for early syphilis and who had thereafter been followed for ten or more years. The incidence of clinically detectable cardiovascular syphilis

was 27.6 percent in those receiving little or no treatment for early syphilis; 13.9 percent when some but inadequate treatment had been given; and no cases were observed among 114 patients who had received adequate treatment. These data have been confirmed by others.

There is some evidence, too, (Disaker and his associates) that adequate metal chemotherapy in late latent syphilis may prevent the development of cardiovascular syphilis. The influence of penicillin in preventing the development of cardiovascular syphilis will be undeterminable for two or more decades.

It has been repeatedly pointed out by many investigators that the best hope of therapeutic success in cardiovascular syphilis lies largely in the recognition of aortic involvement before the development of valvular insufficiency or sacular aneurysm. Necropsy studies from many medical centers have confirmed the fact that from 80 to 90 percent of patients with long-standing syphilitic infections, inadequately treated during the early stages, show pathologic evidence of syphilitic aortitis. It is a reasonable presumption, therefore, that in any patient who has had syphilis ten or more years, microscopic lesions of the aortic wall due to syphilitic infection are actually present. The majority of patients with long-standing syphilis may therefore be assumed to have subclinical aortitis, unrecognizable by symptoms, physical signs, or radiologic evidence. The question of importance is the number of these who do develop clinical evidence sufficient to justify the diagnosis.

In a patient with known late syphilis (i.e., of more than four years' duration) and in the absence of hypertension, extensive arteriosclerosis, or rheumatic mitral heart disease, the symptoms or signs of uncomplicated syphilitic aortitis may include:

1. Roentgenologic demonstration of dilatation, increased density, and loss of elasticity of the first portion of the aorta. This should be by fluoroscopy, the use of the oblique position, or roentgenkymography. It cannot rest on the routine postero-anterior teleroentgenogram and Vaquez-Bordet measurements of aortic width, nor on other methods of aortic mensuration, unless distortion be extreme.
2. Heart failure or lowered cardiac reserve in the absence of hypertension or valvular disease. Failure may be either congestive or anginal; paroxysmal dyspnea is probably an anginal equivalent; and lowered cardiac reserve usually first reveals itself by dyspnea on exertion.
3. Localized substernal pain (to be differentiated from the pain of true angina of effort) which characteristically is dull, aching, relatively inconstant, and is neither influenced by exertion nor referred down the arms.
4. Characteristic changes in the second aortic sound. Accentuation in contrast to other heart sounds is the rule, more especially an alteration in quality, best described as approaching a pure musical note.

The available evidence indicates that an experienced and duly suspicious observer can make the clinical diagnosis of uncomplicated aortitis successfully and accurately, as demonstrated by subsequent necropsy findings, in a fair proportion of patients with this condition, but that the diagnosis rests on a combined evaluation of relatively insignificant symptoms, physical signs, and highly expert radiologic study.

Wile and Snow emphasize that both aortic insufficiency and saccular aneurysm may be entirely symptomless conditions discovered only on routine physical examination. McDermott, Tompsett, and Webster disagree with the picture of aortic insufficiency described in standard textbooks as one of rapid development of symptoms and signs of cardiac insufficiency, and with the general impression that survival after the development of symptoms, or after recognition of the lesion, is usually a matter of only one or two years. Among 2,718 syphilitic patients examined at the Cornell Clinic from 1936 to 1941, McDermott's group found the incidence of syphilitic aortic insufficiency without aneurysm to be 3.4 percent. One half of these patients with aortic regurgitation were unaware of any symptoms of cardiac insufficiency at the time of diagnosis. Only one third of them sought medical care because of symptoms referable to the heart. Fifty-eight percent came to the hospital for noncardiac complaints, and 8 percent were brought under medical care by the routine serologic testing of supposedly well people. The width of the aorta, as judged from appropriate radiologic examinations, was normal in 43 percent of these patients with aortic insufficiency. Twenty-eight of the asymptomatic patients were followed for more than two years during which only two died of heart disease, and only two others developed symptoms.

Reader, Romeo, Webster, and McDermott have re-examined their material after a further five years. Forty-three of their original patients have been followed for from two to sixteen years. All but four of them were white, the majority elderly, and all but six well treated for syphilis after the recognition of the cardiac lesion. The asymptomatic phase of aortic regurgitation could be measured in years (from two to ten, average six years); and even after the development of symptoms, patients may maintain compensation, continue to work, and live from two to fourteen years (average 5.6 years).

These data indicate that both syphilitic aortic insufficiency and aneurysm may frequently be present in clinically recognizable form for long periods before the development of symptoms, and that the prognosis for average duration of life is far better than is usually believed to be the rule, especially if anti-syphilitic treatment is given.

Studies within the past ten years in which routine electrocardiograms have been made on patients with syphilitic infections of varying duration, with and without clinical evidence of syphilitic heart disease, and before and after treatment may be summarized by the brief statement that there are no characteristic electrocardiographic changes associated with syphilitic heart disease.

However, the electrocardiogram makes it possible to recognize, in a fairly high proportion of cases and with a reasonable degree of accuracy, the presence of involvement of one or both coronary ostia, which is probably much more frequent than has hitherto been suspected.

One of the extraordinary mysteries of syphilis, for which no reasonable explanation has as yet been advanced, is the almost complete absence of clinical or autopsy evidence of syphilitic aortitis or other forms of syphilitic cardiac disease in patients with the congenital infection, as contrasted to its almost uniform presence in those with the late acquired disease. Hinrichsen points out that in infantile congenital syphilis there may be definite myocardial lesions of two types, namely, (1) interstitial and (2) nodular myocarditis, in each of which spirochetes can be demonstrated. On the other hand, in children surviving infancy and falling therefore into the diagnostic category of late congenital syphilis, there is no evidence whatever that the congenital infection produces valvular heart lesions. The role of congenital syphilis in the production of aortitis and aneurysm and of congenital malformations of the heart has not been definitely determined, but is certainly minimal. In rare instances the congenital infection may produce syphilitic arteritis of the peripheral, particularly cerebral, arteries.

In view of the uncertainty of diagnosis of uncomplicated syphilitic aortitis, information concerning the effect of antisyphilitic treatment must be sought from patients in whom the clinical diagnosis is as nearly as possible verified by the presence of aortic regurgitation, saccular aneurysm, or both. Two methods of study, and only two, seem applicable.

The first is a comparison of the pathologic findings in the diseased aorta in untreated as compared with adequately treated patients. The studies that have been carried out prove that a static scar may be substituted for progressive inflammation.

The second approach is a clinical study of the effect of treatment in terms of symptomatic relief and prolongation of life span.

There are available in the world literature, now, nearly forty years after the first introduction of salvarsan by Ehrlich and the initiation of effective metal chemotherapy, only three comparable, and reasonably statistically reliable studies of the effect of antisyphilitic therapy in cardiovascular syphilis. These are by Grant, Padget and Moore, and Stratton.

Depending on the biostatistical method employed, even Grant's data are not strictly comparable with the other two series. Based on 171 cases of aortic regurgitation followed for ten years or until death, Grant indicates that the mortality rate is higher, and especially so from cardiovascular syphilis, in patients untreated or inadequately treated (with potassium iodide only) than in those given

something approaching reasonable arsenic and heavy metal therapy; and that the proportion of patients still living, uneventfully and unchanged, after ten years is higher in the treated group. If, however, Grant's material is reanalyzed on the basis of average duration of life after onset of symptoms, limiting the analysis to patients already dead, there is no difference in the two groups (89 months in 29 treated patients, 87 months in 89 untreated patients). The average duration of life in Grant's untreated group is greater than in treated patients in the two American series. There is, however, a significant difference in the clinical material. Grant's patients were all white males, British Army pensioners, who were able to lead an essentially sedentary life. In the two American series, the patients were predominantly Negro laborers, in whom the unfavorable influence of hard physical work was repeatedly evident.

The data of Padgett and Moore and of Stratton, combined and refigured to show the average duration of life in 60 patients with saccular aneurysm (32 untreated, 28 treated) and 91 patients with aortic regurgitation (51 untreated, 40 treated), all of whom lived at least one year after the onset of symptoms or recognition of the lesion, but all of whom were dead at the time of study, indicate that life span may be approximately doubled by the factor of treatment. The actual figures are for aneurysm untreated, 41 months, treated, 74 months; aortic regurgitation untreated, 45 months; treated, 75 months.

The data of Reader and his associates cannot be compared for lack of pertinent information, but they also strongly suggest that antisyphilitic treatment is effective in prolonging life.

All these results were obtained with prolonged cautious treatment with arsenic, bismuth and mercury.

Whether and how to use penicillin in the treatment of cardiovascular syphilis is a problem which confronts both investigator and practitioner.

The harm, if any, falls into two possible categories: the Jarisch-Herxheimer reaction (therapeutic shock) and the therapeutic paradox (Wile). Concerning the latter, the author believes, on the basis of experience with metal chemotherapy, that except for the development of a regurgitant murmur produced by distortion of an aortic cusp from the scarring which accompanies healing (the substitution of a static for a progressive lesion), there is no such clear-cut entity. It cannot be proved that congestive heart failure appearing for the first time after treatment is due to that treatment, rather than to other factors such as physical stress. In the opinion of the author, fear of the therapeutic paradox has been exaggerated and there is no greater danger from it after penicillin than after arsenic and bismuth.

The Herxheimer reaction is, however, another and more serious matter. This reaction occurs in all types of syphilis after penicillin, arsenic, and to a

much lesser extent after bismuth and mercury. Although the point is not thoroughly documented, it is probably more frequent and more severe in all types of syphilis after penicillin than after arsenic. It is also more frequent and more severe in early than in late syphilis, though it may occur unpredictably in any stage of the infection. The reaction appears within from 6 to 12 hours after the initiation of treatment, and lasts from 6 to 24 hours. It is both systemic (chills, fever, malaise) and focal (increased flare in local lesions, with edema and cellular infiltration). Its focal component has long been recognized as important in cardiovascular syphilis. The too vigorous initiation of treatment with arsenic has led to sudden death within a few hours from aneurysmal rupture or coronary occlusion, the latter from increased swelling of a syphilitic plaque at a coronary ostium. With the metals, therefore, it is customary to give preparatory treatment with bismuth or mercury and potassium iodide for some weeks before starting arsenic, on the theory that these more slowly acting drugs may prevent a later Herxheimer reaction from arsenic, which is then begun, if at all, in very minute doses.

Although proof has never been forthcoming, it has been generally assumed that the Herxheimer reaction was due to the sudden destruction of large numbers of spirochetes with the liberation into the tissues of their split products or endotoxins. Recent studies with penicillin in the clinic have thrown some doubt on this hypothesis. In early syphilis, Farmer has shown that (1) the incidence rate of febrile Herxheimer reactions is only 50 percent, instead of the expected 100 percent; (2) reactions were observed with equal frequency and severity in seronegative or seropositive primary, or in early secondary syphilis; and are therefore probably not related to the number of spirochetes destroyed by the initial dose; (3) with penicillin, the febrile reaction is an all or none phenomenon, apparently not related to dosage. With minute doses (from 1 to 5 units per kilogram) it does not occur, but with doses ranging from 10 to 120,000 units per kilogram (e.g., single dose from 700 to 850,000 units) the frequency and severity of the reaction are identical. This is probably unlike the situation with arsenic, in which frequency and severity seem to be related to dosage, and in which reactions may be avoided by the initial use of small doses; and (4) with penicillin, febrile reactions occurred after doses too small to render early lesions dark-field negative.

If analogy can be drawn between early and late syphilis, these data are important to the use of penicillin in cardiovascular syphilis, since they suggest that the Herxheimer reaction can neither be avoided nor minimized by the initiation of treatment with small doses.

The patients with cardiovascular syphilis who have received the penicillin are divisible into two categories, namely, those few treated with foreknowledge that aortic regurgitation or saccular aneurysm was actually present, and a vastly larger number with various forms of late syphilis, especially neurosyphilis, in whom cardiovascular syphilis was not definitely recognized clinically but may

be presumed (from previous pathologic studies) to have been present. In all, many thousands of persons with syphilitic aortitis must have received the drug.

Only four case reports of deaths caused by supposed Herxheimer reactions have so far been published and none of these is at all convincing. Maxwell has observed a patient who, unrecognized during life as having syphilitic aortitis, died from rupture of the aorta into the esophagus, occurring through a syphilitic plaque, forty-eight hours after the initiation of penicillin treatment and the administration of a total of 700,000 units.

Tucker and Farmer have presented a deliberate study of the Herxheimer reaction in thirty patients with cardiovascular syphilis. Twenty-four of these had aortic regurgitation, six saccular aneurysm. In nine of the total number, penicillin treatment was initiated with a series of very small doses, ranging from 500 to 3,000 units. In twenty-one, initial dosage was large, from 25,000 to 100,000 units. One of those given the initial small dosage, and four who received large doses, developed febrile Herxheimer reactions; and all five of these had associated neurosyphilis. No patient in either group developed cardiovascular symptoms not previously present; nor were there any detectable changes in serial electrocardiograms, leucocyte counts, or sedimentation rates.

It is probable, therefore, that the risk of the Herxheimer reaction from penicillin in cardiovascular syphilis has been greatly exaggerated. Nevertheless, and until further evidence is forthcoming, the Syphilis Study Section of the National Institutes of Health remains cautious and has stated that in syphilitic aortitis with aortic regurgitation, saccular aneurysm, or obvious or masked coronary or myocardial disease, it may be advisable to withhold penicillin altogether, or at least until after heavy metal preparatory treatment has been given. Although the author shares responsibility for that statement, he does not wholly subscribe to it and believes that it is essential to employ penicillin in the treatment of cardiovascular syphilis at least on an investigative basis in order to outline clearly its risks and, more important, its benefits, if any.

The rationale for the use of penicillin in cardiovascular syphilis is so far wholly by analogy. Because the drug is of value in healing other early or late lesions of syphilis, there is every reason to believe that it should heal lesions in the aorta. However, in view of what has already been said concerning the difficulties of evaluating treatment methods in this condition, it is clear that decades must pass before final and accurate information is available.

Fien, a co-worker of the author, has made a preliminary survey of penicillin-treated patients. These are 6 with aneurysm and 25 with aortic regurgitation. Of the former, 2 are dead, 15 and 158 days, respectively, after completion of penicillin treatment, and in both cases from rupture of the aneurysm. The remaining 4 have been followed for from 429 to 773 days after treatment. Of these, two who were never in congestive failure are asymptomatic. One, in failure

before treatment, has been on the borderline of cardiac reserve since and is in a hospital for chronic diseases. The fourth, not previously decompensated, went into congestive failure four months after penicillin, but is now well regulated on digitalis. Of the 25 patients with aortic regurgitation, 4 have died, at periods, ranging from 21 to 499 days after penicillin. Three of these, certainly, and one, probably, died from syphilitic heart disease and in congestive failure. The 21 survivors have been followed from 158 to 1,243 days (average 567 days - about 18 months). Fifteen had never been in failure before penicillin, and have not developed it since. Of the 6 who were in failure prior to treatment, 3 are still cardiac invalids; the other 3 are doing well from this point of view.

These data are of course insufficient to permit conclusions as to the value of penicillin in cardiovascular syphilis. Much further study is necessary. (Am. J. Syph., Gonorr. & Ven. Dis., Jan. '49, J. E. Moore)

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Effect of Prophylactically Administered Penicillin on Incidence of Bacteremia Following Extraction of Teeth: The frequency of bacteremia following the extraction of teeth and its importance in the development of bacterial endocarditis have been established both experimentally and clinically. Although the results obtained by sulfonamide prophylaxis were encouraging, cases of bacterial endocarditis were observed after premedication with the sulfonamide drugs. Because penicillin is superior to sulfonamide compounds in the treatment of endocarditis, it seemed advisable to the authors to employ this antibiotic in an attempt to prevent the bacteremia which follows dental extraction.

Patients who were to have teeth extracted were placed in two groups, one to receive penicillin before operation and the other to serve as a control. In nearly every instance, the patient had been admitted to one of the services of a general hospital for some other illness, and the need for dental extraction was usually incidental. All types of patients were included in the study, except that no one was included who had rheumatic or congenital heart disease or an infectious disease which was likely to be accompanied by bacteremia. There was no selection of patients according to age, color, sex, number of teeth to be extracted or condition of the gums. Patients were not included in the study if they had received a chemotherapeutic or antibiotic agent during the previous twenty-four hours.

The authors decided to employ a preparation of penicillin which could be administered simply in the private practice of a dentist or physician, and an amount which would assure a peak concentration in the blood at the time of extraction and maintain an adequate concentration for a maximum period of time. On the basis of previous work, a dose of 600,000 units of penicillin in peanut oil and beeswax given from three to four hours before extraction was selected as best satisfying those requirements.

The purpose was to employ all of the procedures known to decrease the incidence of bacteremia and, at the same time, to utilize measures which would facilitate the growth of any bacteria that reached the blood. Accordingly, the authors decided to obtain local anesthesia by means of procaine hydrochloride, to which had been added epinephrine hydrochloride in a dilution of 1:25,000, employing infiltration, alone or combined with the conduction method, depending on the location of the tooth. Local infiltration anesthesia has been shown to decrease the incidence of bacteremia. Feldman and Trace suggested that the use of a local anesthetic causes compression of the blood vessels and lymphatics and minimizes dissemination of any bacteria present. In rabbits, procaine is reported to increase the bactericidal and phagocytic power of the blood and thus to act both as a systemic and as a local barrier to the entrance of organisms into the circulation. Furthermore, epinephrine, by its vasoconstricting action, decreases the possibility of the bacteria gaining access to the blood stream.

Sixty-five patients received the penicillin and 65 did not. Extraction was accomplished by the elevator-forceps technic. Blood cultures in duplicate were obtained immediately, and ten, and thirty minutes after extraction, incubated both aerobically and anaerobically and studied for the presence of bacteria.

When all the organisms isolated were considered, 46 percent of the patients in the control group and 37 percent of the patients in the penicillin-treated group were found to have bacteremia. When alpha and gamma streptococci alone were considered, a statistically significant reduction in the incidence of bacteremia, from 34 to 15 percent, was observed with the use of penicillin. Six patients in the control group had positive cultures for the same organism at more than one of the periods studied. Only 2 patients in the penicillin-treated series had bacteremia at more than one period.

The incidence of bacteremia could not be correlated with age, sex, race, state of oral hygiene or number of teeth extracted. The number of positive cultures was greater, however, the more extensive the surgical procedure.

Seven patients with healed rheumatic or bacterial endocarditis had dental extractions on 11 occasions, with penicillin administered prophylactically. A transient bacteremia occurred in 4 patients.

Glaser and his associates recently reported a study in which 40 patients were given large doses of penicillin over a twenty-four hour period before extraction and an equal number served as controls. Blood was taken for culture before and immediately after extraction. Sixty percent of the control patients were found to have alpha or gamma streptococci in the postextraction culture, whereas the incidence was 40 percent in the penicillin-treated group. In the control group the alpha streptococci predominated, whereas in the penicillin-treated group the gamma streptococci were found more frequently. In patients with normal gums the use of penicillin did not result in a significant decrease

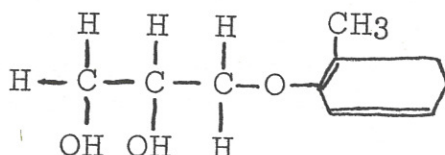
in the incidence of bacteremia after the extraction of teeth. On the other hand, in the patients with gingivitis or pyorrhea the dosage schedule of penicillin employed resulted in a definite decrease in the incidence of bacteremia. These investigators concluded that in patients with rheumatic or congenital heart disease penicillin should be given in large doses for at least twenty-four hours before extraction and should be continued for from 2 to 3 days thereafter. In patients with normal gums the penicillin may be given before extraction and continued for the same period.

Because the bacteremia following dental extraction is of such importance, it is believed that certain principles in the management of patients with known rheumatic or congenital heart disease contemplating dental extractions are worthy of emphasis. Patients who are to have extractions should be questioned carefully concerning a previous history of rheumatic fever, chorea, joint pains, growing pains, unexplained periods of fever, frequent sore throats, scarlet fever or any manifestation of a rheumatic diathesis. In the presence of a suggestive, and certainly with a definite, history of rheumatic fever, the patient should be examined for the presence of valvular heart disease before having the dental work undertaken. Patients with a history of cardiac difficulties, such as dyspnea or cyanosis, indicative of congenital heart disease should be similarly managed.

The present study, in conjunction with that of Glaser and his associates, indicates that the incidence of bacteremia caused by alpha and gamma streptococci can be significantly reduced by the use of penicillin before extraction. The optimal dose and time of administration remain to be worked out. On the basis of present knowledge, it seems that the best procedure would be one that assured the presence of penicillin in the gums and adjacent tissues for twenty-four hours before extraction, a peak concentration of penicillin in the blood during and immediately after the extraction and a bactericidal concentration in the blood for at least twenty-four hours after extraction. A practical program which would accomplish this objective would consist of an injection of 300,000 units of penicillin in wax and oil (or a similar preparation) about twenty-four hours before extraction was contemplated. Three to four hours before the extraction an additional dose of 600,000 units of penicillin in wax and oil should be administered. (Arch. Int. Med., June '48, H. L. Hirsh et al.)

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Effects of Myanesin Upon the Central Nervous System: Myanesin, one of a series of alpha substituted glycerol ethers was investigated by Berger and Bradley who found that it produced in animals a profound muscular relaxation



without unconsciousness. In large doses they noted analgesia, ataxia, arousable sleep and complete paralysis. It is a local anesthetic. They thought that the chief action of the drug was upon reflex excitability of the spinal cord, because the convulsions of strychnine were effectively prevented and those from metrazol (leptazol), supposedly acting upon higher centers, were much less influenced. With large doses a peripheral curare-like effect was demonstrated in nerve-muscle preparations. Mallinson first employed myanesin in human beings to aid relaxation in general anesthesia.

The chief clinical interest in the compound stems from the observation by Stephen and Chandy that the drug abolished the tremors and rigidity of Parkinsonism and reduced the movements of choreo-athetosis at a dose which did not impair strength or consciousness. In this action the drug is unique. Electroencephalogram patterns of their patients were unaltered by the drug. From their observations they concluded that the chief site of action was upon structures lying between the cortex and the spinal cord. Schlesinger et al. found, in addition, with somewhat larger doses, a depressant effect on spinal cord reflexes.

The authors have been investigating the effect of myanesin upon various pathological states in order to determine its sites and modes of action and to evaluate its therapeutic possibilities. The authors have been able to confirm several of Stephen and Chandy's observations and to add some others of interest. The usual common effects of the dose employed consisted of a subjective sense of warmth, relaxation and slight giddiness, but not impairment of mental faculties. Two patients became faint when placed upright while under drug action. Nystagmus, slurred speech and loss of eye convergence were ordinarily observed. Normal electroencephalographic patterns were unaltered.

The tremor of Parkinsonism was abolished (in 7 patients) and choreo-athetotic movements were suppressed greatly or completely (in 4 patients). Rigidity was greatly decreased or abolished in these patients, but strength was unaltered and tendon reflexes were little affected. Senile tremor was greatly improved. On the other hand, the intention tremor of multiple sclerosis was increased (in 2 cases). Two cases of chorea (1 Huntington's and 1 congenital) were unaltered. Brief discharges associated with anterior horn cell disease were unaffected. No alteration of organic facial hemispasm or of fasciculations in amyotrophic lateral sclerosis was observed. In one patient with tetanus the spasms were abolished.

Strength was unaltered in 16 patients without pre-existing weakness, but 2 patients with multiple sclerosis developed a profound increase in weakness in the lower extremities although the upper extremities were unaffected. At the same time there was a decrease in tone. One tabetic patient had an increase in his ataxia and perhaps some decrease in strength. It is apparent that weakness is more easily developed in the presence of pre-existing disease of the pyramidal, and possibly other, systems.

Spontaneous pain was abolished and the exaggerated second-pain in response to pinprick of a tabetic person was reduced, without loss of pinprick perception. Causalgic pain was relieved (1 patient) for a short time and improved for 24 hours. Phantom limb pain, in contrast, was unaffected (1 patient). Stephen and Chandy, and Schlesinger et al. had noted an effect upon pain.

These clinical observations suggest that myanesin in the doses used, has a differential action upon the basal ganglia, brain stem and perhaps thalamus.

To test further the possibility that pathological discharges from the thalamus or related structures might be influenced by this agent, the authors have studied the electroencephalograms of persons with petit mal, in whom large areas of brain cortex are fired simultaneously, possibly from thalamic or subthalamic nuclei. In 6 patients with true petit mal without general seizures these discharges were abolished by this agent. By contrast, convulsive patients with focal cortical abnormalities and 2 patients with petit mal associated with generalized seizures, the so-called petit mal variant of Lennox, and supposedly the result of cortical damage, were unaffected. These observations, taken with the fact that normal electroencephalographic patterns were unaltered by this dose, suggest that myanesin acts in these patients by preventing the discharges arising in subcortical nuclei.

Since improvement in certain psychoses has been obtained by severing the connections of the thalamic nuclei and various parts of the cortex or by a destruction of thalamic nuclei, a trial of this agent which appears to affect the thalamus would seem to be profitable. Preliminary observations on 3 patients have proved of interest. A patient with reactive depression was improved for the period in which the drug was active; a deteriorated negativistic schizophrenic became communicative for the first time in years; and an agitated patient who would not respond became calm and communicative under the action of the drug. These experiences are being extended.

Although said to be effectual orally and intramuscularly in animals, the authors have used the intravenous route. Injection of a 1 or 2 percent solution rapidly up to 1 Gm. establishes the action. From this dose the effect lasts a matter of from a few minutes to 1 hour. To maintain action after the initial dose it is necessary to infuse at about 1 mg. per kilogram body weight per minute. This is about the amount required to maintain a constant blood level in animals. It seems likely that effective action requires the maintenance of a critical blood level of an agent which is rapidly inactivated. The maximum total dose the authors have used is 87 mg. per kilogram body weight.

The authors have observed no untoward reactions. Although the drug is hemolytic, no hemoglobinuria was found and no venous thrombosis has been observed. Jacobs et al. find that it acts as a detergent on red cells.

The action of myanesin appears to be differentially selective for the cluster of subcortical nuclei which make up the basal ganglia, thalamus and brain stem. With increasing dosage the conducting mechanisms of the spinal cord, both motor and sensory, are blocked, and cortical activity is depressed. Finally, a peripheral neuromuscular block ensues. But apart from this selective affinity of action, the evidence from pathological cases suggests that the drug cuts down any repetitious, prolonged or grouped discharge. Tremor, athetosis, rigidity, spasticity, the spasm of tetanus, and prolonged pain, all may be abolished by myanesin at a time when brief twitches, such as choreic jerks and fasciculations and the perception of pinprick are unimpaired. This, in turn, may depend, as with barbiturates, upon a depression of synaptic transmission.

As matters now stand, myanesin may be used, wherever intravenous infusion is feasible, to achieve a transitory relief of tremor, relaxation of tone, and relief of pain. Examples are: as an adjunct to anesthesia and, as Schlesinger et al. suggest, for painful lumbar spasm and manipulation of joints. In the case of Parkinsonism rigidity and tremor and athetosis the drug unquestionably has a greater effect than any other therapy short of narcosis. This fact alone should encourage a search for similar, but longer-acting compounds. The rapid inactivation of the drug still limits its usefulness in chronic conditions. (Am. J. M. Sc., Feb. '49, G. D. Gammon and J. A. Churchill)

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Electrophrenic Respiration. II. Its Use in Man: In a previous investigation it was shown that in the absence of spontaneous respiration artificial respiration could be effectively administered to the cat, dog, monkey, and rabbit by electrical stimulation of one or both phrenic nerves. During the development of the applications of the technic, an opportunity occurred for testing the method in man. A patient with severe, chronic, diaphragmatic flutter was operated on for the purpose of (1) crushing the left phrenic nerve and (2) temporarily blocking the right phrenic with procaine. At the time of operation a single, slender, multiple-strand, plastic-covered wire was spirally wound around the right phrenic nerve in its exposed portion and the other end of the lead wire was brought out through a simple needle puncture wound about 2 cm. lateral to the site of incision. The operation was performed under local anesthesia. Five hours later, electrophrenic respiration was begun.

An ECG plate secured at the wrist functioned as an indifferent electrode for the single stimulating electrode on the phrenic nerve. The stimulating current was derived from a Grass stimulator set for a frequency of 40 per sec. and an impulse duration of 2 milliseconds. The current was run through a rotating potentiometer which rhythmically varied the voltage in such a way as

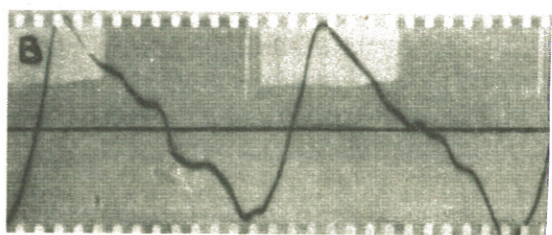
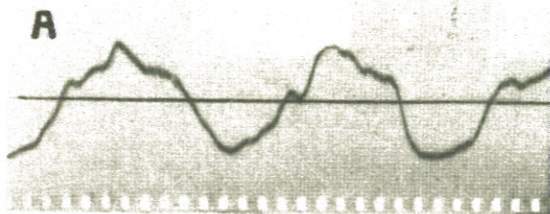
to cause the diaphragm to perform a gradual contraction and relaxation similar to that which it performs during spontaneous breathing.

Air flow patterns were obtained with the pneumotachograph. From the pneumotachogram, it is possible to derive information related not only to the rate and contour of the respiratory pattern but also precise values for the patient's ventilation volume. The level of arterial oxygen saturation was observed throughout the period of phrenic nerve stimulation by means of the Millikan oximeter.

The experiments on this patient were designed (1) to ascertain whether electrophrenic respiration could maintain minute volumes equal to or greater than the spontaneous resting minute volume with submaximal stimulation of one phrenic nerve, (2) to ascertain the ease with which a smooth diaphragmatic motion can be obtained in man, (3) to find out if the unanesthetized patient would cease spontaneous respiratory activity when adequate aeration was supplied by means of phrenic stimulation (as was previously found to be the case in the experimental animal under anesthesia), (4) to estimate the amount of pain or discomfort produced by effective electrical stimulation of the phrenic nerve, and (5) to ascertain whether adequate arterial oxygen saturation could be maintained with the submaximal stimulation of one phrenic nerve.

Pneumotachograms of (A) spontaneous respiration and (B) electrophrenic respiration appear below. An exchange of air significantly larger than the

patient's spontaneous exchange was readily achieved at a rate slower than the spontaneous rate. A still larger exchange of air resulted from maximal stimulation. It was established in this patient, as in the experimental animal, that the depth of respiration is proportional to the peak voltage applied.



A, Pneumotachogram of Spontaneous Respiration

B, Pneumotachogram During Electrophrenic Respiration

The diaphragmatic contraction produced by electrical stimulation of the phrenic nerve in this patient was a smooth motion. (The minor irregularities in the record during diaphragmatic relaxation were due to the diaphragmatic flutter.) A smooth inspiratory curve was, in fact, predicted from the theoretical basis on which electrophrenic respiration is based; namely, that increasingly forceful contraction of the diaphragm results from the spread of current to include more and more fibers of the phrenic nerve as the voltage

is increased. Because the phrenic nerve in man is a single trunk and is considerably larger than that of the experimental animal, a graded voltage spread is more easily and smoothly obtained. As observed visually, the movement of the right diaphragm resulting from phrenic nerve stimulation closely resembled that seen during spontaneous respiration.

It was apparent from simple observation of the patient that during artificial respiration there was no respiratory effort other than that of the right diaphragm, which resulted from electrical stimulation. A pneumotachogram of spontaneous respiration interrupted by the onset of electrical artificial respiration showed no evidence that spontaneous respiratory activity occurred after phrenic nerve stimulation had been started. The regularity of the tracing indicated that the patient was not contributing to the respiratory effort. The reverse sequence was employed to find out whether, upon abruptly terminating artificial respiration, the lack of spontaneous respiratory activity would be apparent from the lack of air flow as registered on the pneumotachogram. Artificial respiration was stopped at the signal and no respiratory activity was present until the apnea had persisted for over 16 seconds. Breathing then returned with a gradual increase in amplitude until it regained its pre-stimulus contours. This interesting observation, namely, that the individual completely relinquishes spontaneous control of respiration while on electrophrenic respiration, is not yet fully explained. Animal experiments in which blood gas tensions were observed indicate that the prompt cessation of spontaneous respiration is not due to a fall in carbon dioxide brought about by overventilation. The neural pathways involved in this phenomenon are being investigated.

During phrenic nerve stimulation the patient experienced discomfort referred to the right shoulder along the ridge of the trapezius muscle. This information was obtained only on direct questioning and was never volunteered. The patient did not appear to be in pain and fell asleep several times during the longer periods of artificial respiration. Conclusions concerning the degree and importance of the intensity of the discomfort produced will have to be deferred until a variety of patients have been studied.

It was thought, prior to the experience with this patient, that the relatively stable mediastinum of the human subject might prevent the adequate aeration of the contralateral lung when only one phrenic nerve was stimulated, even though reasonable respiratory minute volumes were achieved. In order to obtain evidence in this matter, arterial oxygen saturation (by the oximeter method) was observed during spontaneous respiration and during artificial respiration in the absence of spontaneous respiratory activity. It is clear that a small but definite rise in arterial saturation occurred within 60 seconds of the onset of electrophrenic respiration. A rise of one percent in saturation at the upper range of the oxyhemoglobin dissociation curve indicates a rise of 10 mm. Hg or more in the mean effective alveolar partial pressure of oxygen. This signifies an improvement in lung ventilation out of proportion to a one percent rise in oxygen saturation.

Artificial respiration by phrenic nerve stimulation was induced in this patient for several periods varying in length from 5 to 76 minutes on two occasions during the 5 days following electrode application. The procedure apparently resulted in no functional damage to the nerve, since fluoroscopic examination of spontaneous diaphragmatic activity on the day of electrode removal revealed excursions equal in amplitude to those observed before the experiment. (J. Clin. Investigation, Jan. '49, J. L. Whittenberger et al.)

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The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent, and Sanguinous Pleural Exudations: The possibility has been explored of utilizing two of the defined products elaborated by hemolytic streptococci that have the unique capacity of causing rapid lysis of the solid elements (fibrin and nucleoprotein) that are significant parts of exudates. Christensen has described additional steps in the purification of the materials employed and has given quantitative methods of measurement of various increments concerned in the fibrinolytic system, including trypsin inhibitor and specific antibodies, which have been employed in this study.

The results described in this article were obtained by the injection of concentrated and partially purified preparations derived from broth cultures of hemolytic streptococci into the pleural cavity of selected patients who were suffering from different types of diseases that gave rise to pleural exudations. In the study of patients it was first necessary (1) to develop the investigation within nontoxic but effective ranges of doses of the material employed, and (2) to determine whether or not the enzymatic activities of the streptococcal products were effectively operative when introduced directly into the site of the disease in the patients; this article is essentially limited to findings that are pertinent to these two aspects.

It was found that the enzymatic activities being studied could be utilized to produce changes in fibrinous, purulent and sanguinous exudations within the pleural cavities of patients. Thus through the mediation of substances elaborated by hemolytic streptococci, fibrin is caused to undergo lysis; fibrinogen is altered so that it no longer can assume the solid form of fibrin; and the coarse sediment of purulent exudate (primarily desoxyribose nucleoprotein) is degraded to a thin solution.

Once it had been well established by detailed preliminary observations that the methods of purification of the streptococcal products developed extensively by Christensen yielded preparations that were progressively less toxic, although maintaining constant or increased potency, a demonstration of the occurrence and degree of action in patients of the active principles - streptokinase and desoxyribose nuclease - became a center of interest. For this purpose quantitative estimations were made of the results of the action of each enzymatic

system on its respective substrate in the areas of disease.

Definitive enzymatic changes of a significant degree were regularly obtained and were demonstrable within an hour after the injection and endured for several days before the effect subsided and disappeared. The phenomenon was a self-limiting one following each injection.

The clinical courses of the patients have been followed by frequent physical, laboratory, and x-ray examinations over extended periods. Following the injections a febrile response occurred not infrequently and there was also evidence of local irritation. Both signs of reaction were, however, transient.

Because the periods in which the action of the concentrates was operative were limited to a few days, striking evidence of favorable alterations of a permanent nature was not expected nor definitely demonstrated except for the results obtained in cases of loculated hemothorax, and in some of the instances of empyema. In patients with hemothorax, it is obvious that consideration must be given to the broad principles and problems of thoracic surgery before the application of the procedure may be most advantageously made.

The desirability of causing the liquefaction of fibrin or of preventing its formation, or of resolving purulent nucleoprotein-containing sediments, would on theoretical grounds depend upon a variety of conditions associated with the pathogenesis and expected evolution of the disease processes to which this method involving lytic activities might be applied. Comparable principles would also be applicable to exudative diseases involving locations in the body other than the pleural area.

If the solid increments constitute part of an advantageous walling off process then the liquefaction of the wall might promote a spread of the infection in its acute phases before the patients' immunity was sufficient to restrain the dissemination of the infection. On the other hand, the same walling off may prevent the introduction of antibacterial reagents of an immunological nature, as well as antibiotic substances, into the field of disease. Under the latter circumstances elimination of the wall might be advantageous. Other sets of conditions concern factors that are involved in the ultimate formation of scar tissue, or of adhesions, and the permanent thickenings that are related to the final organization of infected areas.

The results presented in this article serve as a basis for extending the study. (J. Clin. Investigation, Jan. '49 - W. S. Tillett and S. Sherry)

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Treatment in Basal Cell Epithelioma by Injection of Tissue Extracts: In a previous report (see News Letter of 27 September 1946) the results of treatment

in cases of basal cell epitheliomas with tissue extracts prepared from human spleen and liver were described. The small number of normal human organs available for this work limited the number of patients who could be accepted for treatment.

From the results obtained by various workers in inducing resistance to mouse carcinoma 15091a and mouse sarcoma 180 with heterologous tissue extracts, it seemed likely that extracts of beef spleen and lamb liver, might prove effective in the treatment of human cancer, even though they might be less effective than homologous tissue extracts.

Beef spleens and lamb livers were obtained from freshly slaughtered animals. The liver and the spleen extracts were prepared separately by the same procedure used for the extracts of human tissues. A concentration of tissue extract equivalent to 15 Gm. of tissue was used. The extract was adjusted to a pH from 6.5 to 7 with potassium hydroxide, and boiled for thirty minutes. After standing in the refrigerator overnight the solution was filtered. The extract was then put in serum bottles and was boiled for thirty minutes on each of three successive days. Each sample of extract prepared was tested for toxicity by injecting into a guinea pig the same amount to be used subsequently on a patient. Ill effects were not shown either by the animals or by the patients.

Patients with small basal cell epitheliomas varying from pea size to 3 or 4 cm. across in the longest dimension were selected for this treatment. Before any treatment was given, a biopsy was performed for pathologic diagnosis of the lesion. The patient was then given a series of weekly intradermal injections varying from 0.25 to 2.5 cc. of the extract. At each treatment the lesion was infiltrated, until the lesion and the surrounding tissue for about 1/4 inch (0.64 cm.) became blanched and hard. After the lesion had regressed clinically a post-treatment biopsy was taken to determine whether any malignancy remained.

Results are reported for 24 patients, of whom 3 were treated with human spleen extract, 3 with human liver extract, 12 with beef spleen extract, 5 with lamb liver extract, and one with both human liver and beef spleen extract.

The results obtained in the 21 previous cases and in the present 24 cases are summarized together. Of the seventeen patients treated with human spleen extract there were eleven with complete regression of the lesion, two with slow regression in which the lesion was excised, two in which the lesion had regressed 50 percent and 80 percent, respectively, when last seen, and two failures. Of the ten patients treated with human liver extract, there were seven with complete regression of the lesion, one with slow regression in which the lesion was excised and two in which the lesion had regressed 90 percent when last seen. Of the 12 patients who were treated with beef spleen extract, there were eight

with complete regressions, one with slow regression in which the lesion was excised, one with 90 percent regression when last seen, and two still under treatment with the lesion showing definite regression. In the patient treated with both human liver extract and beef spleen extract, there has been complete regression of the lesion. Of the 5 patients with six lesions (two in one patient) treated with lamb liver extract there were three with complete regressions and three still under treatment with lesions showing from 70 to 90 percent regression.

The present series of lesions included a spinobasal cell epithelioma and a prickle cell epithelioma. These more malignant epitheliomas likewise regressed completely when treated with the tissue extract. (Arch. Dermat. & Syph., Aug. '48, J. C. Amersbach et al.)

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Arctic Sanitation: Strictly speaking, the Arctic comprises that northern section of the world where the ground is permanently frozen and spoken of as permafrost, even though the top layer of soil may thaw during a brief summer period. The southern limit of this permanently frozen ground coincides generally with the northern limit of tree growth - the tree line. However, for the purposes of this paper, the Arctic will be considered as the entire northern area where extreme cold persists throughout a major portion of the year.

Occasional low temperatures alone do not indicate arctic conditions. As low temperatures have occurred in the continental United States as have occurred in the extreme polar regions; but such low temperatures do not persist outside of the Arctic. Wind, lack of forest growth, continued very low temperatures, a short summer, and permanently frozen ground are characteristic of the Arctic.

The general problems of cold weather sanitation are not insurmountable in themselves, but the difficulties that exist are heightened by the combination of the military problems and those resulting from the hostility of the climate, the inefficiency of men working in extreme cold, the difficulty of merely sustaining life, the great distances, and the necessity for shelter. There are no rats and no cockroaches in the Arctic, but there are mosquitoes and many varieties of gnats and biting insects.

Local food supplies for large bodies of men are nonexistent. Shelter is also practically nonexistent, but in time of storm is essential. Snow houses, or igloos, can be constructed for small groups, but not readily for large personnel masses. Travel and transportation over land are possible in the winter but not in the summer. Snowshoes or skis are necessary for winter travel by individuals. Tracked or crawler vehicles are the only kind that can move off the probably ten miles

of hard surfaced roads in the far north. Sleds can be hauled by these vehicles along previously selected trails only during the winter. Fuel, food, and shelter must be taken along; they do not exist in the Arctic.

For 7 or 8 months each year, all lakes and rivers are covered with 6 ft. or more of ice. Small streams are frozen solid. Because the ground also is frozen, there are many problems of water supply. Fixed supplies must be drawn from under the ice cover. This means that the pond or reservoir or other source must be of sufficient capacity to supply all needs for about 8 months, assuming (1) that the top 6 or 8 ft. will freeze, and (2) that there will be no winter inflow. Because many of the smaller arctic lakes and ponds are relatively shallow, the contours between which the water supply can be drawn may need to be determined accurately.

The amount of water required by large permanently fixed groups has not been determined. Estimates of needs range from 5 to 70 gallons per person daily. The former is no doubt inadequate for any normal conditions; design should probably aim at the latter. Water is generally quite plentiful in the Arctic. Though the rainfall is small, it cannot soak into the permanently frozen ground and so stands in pools or runs off.

Water supplies will usually come from surface sources. As yet not enough is known about arctic ground waters to make definite statements regarding them; but there have been difficulties in sinking and maintaining wells through permafrost and in finding adequate supplies of good quality ground water.

The quality of arctic ground waters appears to be good. It is generally clear and without objectionable characteristics. More needs to be known about its chlorine demand and other factors in treatment.

Pumping stations must be designed and constructed with due regard to permafrost conditions. Steam-operated pumps may be desirable as power must be generated locally with fuel, and the steam can be used to heat the water. As drawn from lakes in the winter, water temperature is about 33° F. It is normal practice to raise the temperature to from 40° to 75° F. at the pump.

Distribution and storage offer many problems. Storage tanks are frequently housed to protect them from the cold. The force line from the pumping station to the storage reservoir must be insulated. Circulation is usually provided by a small bleed-off main which takes water from the storage tank and returns it to the pump sump. Fully satisfactory protective methods to prevent pipe lines from freezing have not been developed. The utilidor system, in which the water, sewer, and steam lines are carried in a single concrete box, is costly and has sanitary objections. Service connections also need protection. It must be remembered that all of these lines must be located in ground that is solidly frozen during much or even all of the year.

In the field, in the winter, water must be procured by melting snow or ice, preferably the latter because much more water is obtained from it and more easily. To supply the necessary amount of water, melting devices and fuel must be provided; and to transport the water, insulated containers are necessary. Insulated water carts, simple snow melting devices, and perhaps insulated canteens may be needed.

The need for adequate waste disposal or even of any method of disposal in the field, aside from tossing the wastes off the trail has been questioned. This viewpoint is wholly erroneous. Time-tested practices in sanitation should not be abandoned.

In fixed posts, water-carried sewage disposal is desirable, though indoor chemical toilets have been used with some degree of satisfaction. Sewers are subject to the same problem of freezing as are water mains. They should probably be insulated and a small steam line laid alongside or under the pipe. Treatment plants would probably not be needed because any large personnel groups would probably be located on deep water and disposal by dilution could be employed. If treatment should be necessary, heat will probably have to be provided and the plant structures must be carefully designed for permafrost conditions.

Field disposal of sewage is an unsolved problem as yet. Pits are difficult or impossible to dig in frozen ground. Chemical toilets of the pail type seem promising. Disposable linings for these toilets are being tried, but getting rid of the lining and contents is a problem. Perhaps a chemical can be developed which, when the contents thaw in the summer, will provide effective sterilization. Mere tossing aside of these used containers, especially when the number of men involved is considerable, is certainly open to serious question. Protecting personnel from the weather while using toilet facilities is necessary, and as yet no standard practice has been developed.

There are many mosquitoes during the short arctic summer, also various flies and other biting insects. Mosquito breeding starts as soon as the snow begins to melt; the eggs were laid the previous fall. Although there are probably no mosquito-borne diseases in the Arctic, the problem of comfort is an important one. Area control with DDT and other compounds has been tried. In general, because insects from outside the sprayed area move in very quickly, relief is of short duration, even when a considerable area is treated. Work has been done on the application of insecticides to the snow before melting begins, and results have been promising.

In field service, consideration must be given to such other factors as food, shelter, transportation, and clothing. Developments in shelter and transportation may influence, to a marked extent, the details of sanitation practices. If, for instance, overland transportation is developed beyond that embodied in present ideas, sanitation problems might not be too different from those now encountered in the northern part of the U. S. (Am. J. Pub. Health, Feb. '49, W. A. Hardenbergh)

An Evaluation of Methods of Rewarming Men: It is usually not feasible to provide clothing which will maintain thermal equilibrium for inactive men exposed in extremely cold weather.

Is it better for the soldier who wakes up cold at 0200 hours to climb out of his sleeping bag and run about, or to exaggerate his natural inclination to shiver while rewarming in the bag, or to reach out of his bag and light his Coleman stove? Will the vehicle driver who has become numb with cold be restored more quickly and effectively by running up and down outside, or by toasting himself and his clothing before a fire in a heated shelter, or by simply drinking hot coffee from a vacuum flask while remaining at the steering wheel?

The present study of methods of rewarming men was designed (a) to evaluate the relative efficiency of different methods of rewarming (increasing metabolism, increasing ambient temperature, and increasing insulation) commonly employed by troops operating in cold climates, (b) to determine the effect of selectively heating the face or hands of men exposed to cold, (c) to investigate briefly the effect of glucose or alcohol ingestion in men exposed to cold, and (d) to note evidence of acclimatization in men exposed to cold repeatedly for short periods.

Moderate exercise (walking at 3.5 m.p.h. on a 6.5 percent grade) caused a more rapid regain of body heat than any of the other methods studied. Exposure to higher ambient temperatures resulted in a rapid rise in surface temperature of the body, but in a continued fall in internal temperature; one hour at a room temperature of +80° F. was not sufficient completely to rewarm subjects who had been inactive for one hour at -40° F. Most of the heat was regained during the first hour in the sleeping bag.

Heating the face of men in the cold tended to increase blood flow to the hands and sometimes to the feet. This effect was more consistent in men who had not become thoroughly chilled. Face-warming had little effect on total body heat content. Heating the hands did not significantly affect the surface temperature of other parts of the body.

Under the conditions of this investigation, the ingestion of glucose had little effect on the reactions of men to cold. It slightly delayed the fall in internal temperature. The ingestion of alcohol did not cause significant peripheral vasodilatation in men who had been exposed to cold. It delayed the fall in internal temperature and increased thermal comfort.

The repeated short periods of cold exposure used in this series of experiments did not produce evidence of acclimatization in terms of cooling curves. The subjects appeared to maintain thermal comfort longer as the experiment progressed, and the time elapsed before the onset of shivering was extended. (Environmental Protection Series, Rep. No. 134, 31 Aug. '48, U.S. Army, Office of the Quartermaster General, Military Planning Div., Research and Development Branch, Quartermaster Climatic Research Lab., Lawrence, Mass., A. Ames et al.)

Twenty-Five Year Survival of a Culture of Plague Organisms: A culture of Pasteurella pestis P4-7 was received 11 December 1922, from the Public Health Service plague laboratory in San Francisco where it had been isolated from a California ground squirrel. In June 1923, the culture P4-7 was found to be highly virulent for guinea pigs and white rats. Heart blood of the guinea pigs was cultured by transfer of a few infected drops of blood to slants of plain beef infusion agar, and the growth was subcultured on the same medium until there were 48 infected tubes on which the author has made viability and virulence tests after 10, 20, and 25 years of storage at from 5° to 10° C., without transfer.

In 1943, 33 of the 48 original cork-stoppered tubes inoculated in 1923, and maintained at from 5° to 10° C. without transfer, had been found to contain viable organisms. These cultures were transplanted 25 August 1948, each to a fresh cotton-stoppered slant of horse-meat infusion agar and incubated at room temperature with the result that 25 of the 33 transplants grew promptly and luxuriantly in from 2 to 8 days, but 8 failed to grow and were discarded together with their correspondingly numbered 1923 parent tubes.

Virulence testing of the 25 viable transplants of the 25-year-old cultures consisted of subcutaneous injection on the abdomen of a guinea pig with a platinum loopful of undiluted fresh culture growth collected from the surface of each week-old agar slant. Twenty-five guinea pigs thus inoculated became noticeably sick in from 2 to 4 days, but all, except three which died, gradually recovered by the end of 2 weeks.

The three guinea pigs that died manifested the typical lesions of acute plague - edematous swelling and hemorrhagic injection at the site of inoculation, enlarged softened caseous inguinal lymph nodes, and areas of focal necrosis in the enlarged spleen. Smears of these tissues showed great numbers of typically bipolar-staining bacilli, and the spleen yielded typical cultures of P. pestis.

Low temperature and the presence of moisture are important for the long preservation of viability and virulence of P. pestis. Incubation at 37° C. and the temperature of the tropics rapidly shorten the length of life and virulence of plague organism cultures. Care was exercised to use agar slants liberally supplied with water of condensation. Cotton stoppers were used only during the few days of incubation at room temperature and were then replaced by cork stoppers grasped by mouse-tooth forceps and forcibly introduced after being dipped into a boiling mixture of half paraffin and half vaseline. This tightly-fitting stopper excluded air and prevented any evaporation of the water of condensation. Such tubes stored upright at from 5° to 10° C. and opened only three times in 25 years still maintained approximately their original amount of water of condensation.

The present remainder of the 1923 collection of cultures now consists of 25 numbered tubes stored in the cold room to await tests in future years. Another collection of 40 cork-stoppered cultures numbered from 49 to 88 prepared in 1924 from plague strain P4-7 and identical with the 1923 collection except that they have not been opened since 1924 are stored in the cold room at from 5° to 10° C. awaiting tests for viability and virulence in later years. (Pub. Health Reps., 25 Feb. '49, E. Francis)

Course in Preventive Medicine and Venereal Disease Control: The Bureau of Medicine and Surgery announces the availability of a one-year course in Preventive Medicine and Venereal Disease Control leading to the degree of Master of Public Health at the Johns Hopkins University School of Hygiene and Public Health beginning 1 July 1949.

Requests are desired, in letter form, from interested medical officers of the regular Navy. To receive consideration, requests must reach BuMed prior to 1 April 1949. Provided the time element requires it, requests may be made by dispatch and confirmed by letter. It is necessary for each applicant to provide a three-year service agreement. (Professional Div., BuMed)

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Use of X-Ray Protective Screens in Dental Activities: The article, "Protection of Dental X-Ray Technicians from Irradiation," which appeared on page 23 of the U. S. Navy Medical News Letter, Volume 13, Number 1, dated 14 January 1949, caused numerous requisitions to be submitted to the naval medical supply depots for item #6-128-025 Screen, X-Ray, Protective. Many who requisitioned this x-ray protective screen were apparently not acquainted with the fact that it is 72 inches high, 36 inches wide, 16 inches deep, made of steel, lead, and glass, and costs \$210. It is appropriate for use only in large dental activities that have separate dental roentgenographic sections in which one person may expose more than 30 full-mouth series of films (420 individual films) per week.

Responsible dental officers should determine whether any persons in the dental clinics or services are being exposed to x-rays in sufficient amounts to justify the use of screens before submitting a requisition. (Dental Div., BuMed)

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Matters of Interest Concerning Medical Materiel: The Addenda to the Army-Navy Catalog of Medical Materiel is no longer applicable. Therefore, any item contained in the Army-Navy Catalog of Medical Materiel or subsequent changes thereto may be requisitioned from the appropriate naval medical supply depot provided no restrictions on issue are contained in the description of the item or that the item is not indicated as an Army Only item.

Release of Change Bulletin #3 to the Army-Navy Catalog has been delayed. It is anticipated that this change bulletin will be available about April, 1949.

Attention of all activities is invited to the importance of reporting overages as well as underages on receipt of materiel from naval medical supply depots. There are known instances of overages having been received by field activities for which reports have not been received at the issuing medical supply depot. Attention of all concerned is directed to the fact that the responsibility for reporting overages is the same as for reporting underages.

New policy regarding issues of surgical sponges. Investigation has revealed that many activities will find it more economical and more satisfactory to use commercially prepared surgical sponges than to fold their own from gauze. Accordingly, the restrictions on issues for the below-listed catalog items have been removed and requisitions (nonrecurring) may be submitted to the appropriate medical supply depot for initial stocks. Requisitioning activities should consider the reduction in usage of uncut gauze incident to the use of these new items.

<u>Stock No.</u>	<u>Item</u>	<u>Unit of Issue</u>	<u>Price</u>	<u>Packing & Pkg.</u>
LS 2-038-420	Sponge, Surgical, 2x2, 200's:	Pkg.	\$.45	12/96
LS 2-038-450	Sponge, Surgical, 4x4, 500's:	Pkg.	2.34	-/12
LS 2-038-485	Sponge, Surgical, 4x8, 180's:	Pkg.	1.85	-/12

Requisitioning activities should submit requisition for the Limited Standard items. When stocks of Limited Standard items are depleted the standard items listed below will be substituted by naval medical supply depots:

<u>Stock No.</u>	<u>Item</u>	<u>Unit of Issue</u>	<u>Price</u>	<u>Packing & Pkg.</u>
2-038-415	Sponge, Surgical, 2x2, 100's:	Pkg.	\$.35	50/300
2-038-448	Sponge, Surgical, 4x4, 200's:	Pkg.	1.74	20/60
2-038-480	Sponge, Surgical, 4x8, 100's:	Pkg.	1.40	20/40

Pitocin Ampuls (Stock No. 1-352-350): Substitute for. Commercial sources of Pitocin ampuls (Stock No. 1-352-350) are having considerable difficulty in meeting demands of the Armed Services for this item and from information available, this situation will continue to exist.

The literature offers convincing evidence that, in appropriate dosage, Pituitary, Posterior, Injection (N-LS Stock No. 1-353-000) produces all the effects of subject item and that the side effects are of disadvantage only when contraindicated by hypertension. In view of this, Pituitary, Posterior, Injection, Stock No. 1-353-000, is being made standard by the Navy.

Naval activities are therefore requested to restrict the use of Pitocin ampuls (1-352-350) to those cases in which the use of Pituitary, Posterior, Injection (1-353-000) is considered to be definitely contraindicated. (Materiel Div., BuMed)

Examinations for Appointment in Navy Medical Corps to be Held 4-8 April 1949 at Naval Hospitals: Examinations for the selection of candidates for appointment to the grade of lieutenant (junior grade) in the Medical Corps of the Navy will be conducted at all naval hospitals in continental United States during the period, 4-8 April 1949.

Graduates of approved medical schools in the United States or Canada who have completed intern training in accredited hospitals or who will complete such training within four months of the date of the examination, and who are physically and otherwise qualified, may be examined for appointment as lieutenant (junior grade) in the Navy Medical Corps. Candidates must be less than 32 years of age at the time of appointment.

Candidates will be required to appear before boards of medical examiners and supervisory naval examining boards at the naval hospital nearest their place of residence to demonstrate their physical and professional qualifications for appointment. Following approval by the President of the United States and confirmation by the Senate, selected candidates will be issued appointments and orders assigning them to duty in a naval medical facility for active naval service.

As a result of the authorized additional compensation of \$100 a month for medical officers, a lieutenant (junior grade) in the Medical Corps of the Navy receives pay and allowances totalling \$5,011 a year if married, and \$4,575.50 if without dependents.

Detailed information concerning the form and procedure of application may be obtained from the nearest Naval Officer Procurement Office or from the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C. (Professional Div., BuMed)

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Course in Medical Aspects of Special Weapons and Radioactive Isotopes Available to Reserve Medical Officers: The Bureau of Medicine and Surgery announces the third course of instruction in the medical aspects of special weapons and radioactive isotopes. This course is to be conducted at the U. S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland. It will commence on Monday, 25 April, and end on Saturday, 30 April 1949; it will be similar to the two previous courses.

Inactive Reserve medical officers who desire to attend this course should submit a request for training duty to the commandant of their naval district. All requests should reach the commandant's office prior to 1 April 1949.

The facilities available at the National Naval Medical Center make it necessary to restrict the number in attendance to 210. The Bureau of Naval Personnel has established quotas as follows:

First Naval District.....24	Ninth Naval District.....50
Third Naval District32	Eleventh Naval District..... 2
Fourth Naval District.....20	Twelfth Naval District..... 2
Fifth Naval District18	Thirteenth Naval District..... 2
Sixth Naval District20	Potomac River Naval Command.....12
Eighth Naval District18	Air Operational Training Command.....10

Sleeping quarters at the Center will be provided for many who wish such accommodations. Full messing facilities will be made available. (Personnel Div., BuMed)

* * * * *

Salt Tablets for Use Against Salt Loss from Excessive Perspiration: Impregnated salt tablets first produced through the efforts of the Naval Medical Research Institute have been shown to be more satisfactory than either plain salt and dextrose tablets or enteric-coated salt tablets in the prevention of symptoms due to salt loss from excessive perspiration. Both of these latter two tablets, especially the plain, quickly disintegrating tablets, have been known to cause cramps, diarrhea, nausea, etc. The enteric-coated tablets, developed to overcome these symptoms, do not begin dissolving in the intestinal tract until approximately 4 hours after ingestion so that they do not meet the requirements for promptly supplying salt to the system.

The impregnated tablets begin dissolving immediately, supply a continuous source of salt, and do not cause nausea and other untoward effects.

The Bureau of Supplies and Accounts is stocking impregnated salt tablets (Stock Number 51-S-3019-985) in naval supply depots; they will be obtainable through the supply offices of ships and stations. (Preventive Med. Div., BuMed)

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BuMed-41-bad/NH93/A1-1

4 February 1949

To: The Secretary of Navy
Via: The Chief of Naval Operations

Subj: Establishment of the U. S. Naval Hospital, Beaufort, South Carolina;
Request for

Ref: (a) BuDocks ltr to BuMed NH(86)/N9 C-240A dtd 2 Feb 1949

1. By reference (a), the Bureau of Yards and Docks informed this Bureau that construction of the U. S. Naval Hospital, Beaufort, South Carolina, has been completed to the stage that it could be turned over to the Bureau of Medicine and Surgery on 2 February 1949.

2. It is requested, therefore, that the U. S. Naval Hospital, Beaufort, South Carolina, be established as of 2 February 1949 under a Medical Officer in Command, under the military command and coordination control of the Commandant, Sixth Naval District, and under the management control of the Bureau of Medicine and Surgery.

3. Transfer of personnel now on duty at the U. S. Naval Hospital, Parris Island, South Carolina, to the U. S. Naval Hospital, Beaufort, South Carolina, will be requested at such times as their services are required at the latter hospital.

4. It is estimated that the Beaufort Naval Hospital will be completely equipped, furnished and ready to receive patients sometime in April 1949. When the Beaufort Naval Hospital is ready to accept the transfer of the patients in the Parris Island Naval Hospital, this Bureau will recommend the disestablishment of the latter hospital. --BuMed J. T. Boone

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SecNav, Op24/cj/NH(86)/A4-2, Serial 7P24

10 January 1949

To: All Ships and Stations

Subj: U.S. Naval Medical Unit, Georgia Warm Springs Foundation, Warm Springs, Georgia: Disestablishment of.

1. The following activity is disestablished effective 31 December 1948.

U. S. Naval Medical Unit
Georgia Warm Springs Foundation
Warm Springs, Georgia

4206-800

2. This unit has served its purpose and arrangements have been made for the hospitalization of the small number of patients requiring the advantages at the Foundation without the necessity of keeping naval personal on duty there.

3. Bureaus and offices concerned take necessary action. --SecNav.

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BUMED CIRCULAR LETTER 49-16

15 February 1949

To: All BuMed Management Control Activities

Subj: Personal Service Contracts: Appropriate Use of

Ref: (a) NCPI-35, dated 7 July 1948.

Because of the uncertainty which has arisen concerning the choice of the three methods of procuring personal services of a specialized nature, outside

of regular Civil Service procedures, as provided for by reference (a), there is contained in this letter a discussion of the purpose for which each of the three methods is used.

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BUMED CIRCULAR LETTER 49-17

16 February 1949

To: All Dental Activities

Subj: Oral Pathological Material

1. This letter is sent at the request of the Dental Officer in Command of the U. S. Naval Dental School for the purpose of:

a. Providing skilled assistance in diagnosis of oral lesions.

b. Obtaining cooperation in procuring a larger collection of oral pathological slides and attendant data for teaching and investigating purposes.

2. Addressees are urged to send to the Dental Officer in Command, U. S. Naval Dental School, National Naval Medical Center, Bethesda 14, Maryland, ante-mortem and post-mortem specimens of oral pathological material. When requested, the Naval Dental School will promptly return a report of histological findings (1 week for soft tissues, 10 weeks for material that includes teeth) and a microscopic section of the specimen submitted.

3. The oral pathological material received will be registered in the sender's name. It will be presented in published case reports only with prior permission of the sender, and then with full acknowledgement.

4. It is understood that many activities have already established a satisfactory working relationship for diagnosis with near-by pathological laboratories. In these cases the Naval Dental School would still appreciate receiving, for each case:

- a. Paraffin blocks or microscopic sections.
- b. A complete case history.
- c. A copy of the pathological report.

5. This request is not intended to conflict with BuMed Circular Letter No. 48-107 which requires that medical activities submit specimens from all types of neoplasms to the Tumor Registry at the Naval Medical School. Pathological material which is forwarded to Bethesda under this directive is shared with the Naval Dental School. It is not necessary, therefore, to send duplicate material to the Naval Dental School.

6. Forms and containers will be supplied by the Dental School for convenience in forwarding the specimens. --BuMed. C. A. Swanson

BUMED CIRCULAR LETTER 49-18

17 February 1949

To: MedOfsCom, Naval Hospitals, Continental U. S.

Subj: Study of Civilian Shift Arrangements in Naval Hospitals

Encl: 1. (HW) Work Schedule (General); ten forms.
2. (HW) Work Schedule for Commissary Division; ten forms.
3. (HW) Transportation by Shift; two forms.

It is stated in this letter that BuMed has directed that a committee undertake subject study for the determination of acceptable, efficient, and economical work schedules for civilian employees and that this matter requires considerable attention since it is difficult to adapt the customary Federal policy and practices, with respect to hours of work, to the needs of naval hospitals where nonstandard hours must be maintained without excessive cost to the Government. Instructions are given concerning information that is to be submitted on the enclosures and otherwise by the addressees prior to 31 March 1949.

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BUMED CIRCULAR LETTER 49-19

Joint Letter

24 February 1949

To: Commanders, All Naval Training Centers
Commanding Generals, U. S. Marine Corps Recruit Depots,
Parris Island, S. C. and San Diego, Calif., and
U. S. Marine Corps Barracks, Camp Lejeune, N. C.

Subj: Procedure for Disposition of Male Enlisted and Inducted Recruits and Authority to Take Final Action on Aptitude Board Reports.

This letter from Chief of BuPers, Chief of BuMed, and Commandant, MarCorps, lists 13 references, consists of approximately 7 pages of information and instructions, and includes one enclosure.

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BUMED CIRCULAR LETTER 49-20

Joint Letter

24 February 1949

To: Commanders, All U. S. Naval Shipyards
(Airmail, Pearl Harbor)

Subj: Medical Department. Standard Organization Chart and Standard Shipyard Regulations.

This letter from the Chief of BuShips and the Chief of BuMed shows 2 references and 2 enclosures.

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BUMED CIRCULAR LETTER 49-21 Joint Letter 24 February 1949

To: Commanders, All U. S. Naval Shipyards
 (Airmail, Pearl Harbor)

Subj: Dental Department, Standard Organization Chart and Standard Shipyard Regulations.

This letter from the Chief of BuShips and the Chief of BuMed shows 2 references and 2 enclosures.

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BUMED CIRCULAR LETTER 49-22 24 February 1949

To: All Ships and Stations

Subj: Secret Reports, "War Weariness" and "Attrition," dated April 1945; Declassification of.

Refs: (a) CNO ltr, Op-542-C-dm, A6-8, Serial: 751P542, dated 2 Dec 1948.
 (b) Secret Report, "War Weariness," April 1945.
 (c) Secret Report, "Attrition," April 1945.

1. Secret reports, "War Weariness" and "Attrition," dated April 1945 are hereby declassified to Confidential in accordance with reference (a).

2. The section of reference (c) entitled "Analysis of Pilot Turnover in 14 CV Squadrons," is hereby declassified to Open in accordance with reference (a).

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-23 24 February 1949

To: All Ships and Stations

Subj: BuMed Circular Letters; Cancellation of Several

In this letter which appears in the Navy Department Bulletin of 28 February, certain BuMed circular letters are canceled because the subjects concerned therein are now covered in the indicated portions of the Manual of the Medical Department, 1945, and changes thereof.

BUMED CIRCULAR LETTER 49-24

24 February 1949

To: All Holders of the Bulletin of Bureau of Medicine and Surgery Circular Letters, NavMed-937.

Subj: BuMed Circular Letters: Cancellation of Several.

1. The following BuMed Circular Letters are hereby canceled for the reasons indicated:

<u>C/L NO.</u>	<u>Reason for Cancellation</u>
44-47	Current instructions in Par. 16B22, <u>Manual of the Medical Department</u> , 1945.
46-89	In view of Military Air Transport Service.
46-163	Submission of Weekly Morbidity Report suspended by BuMed C/L No. 48-44.
48-2	Current instructions in Par. 12B11.6, <u>Manual of the Medical Department</u> , 1945 (Advance Change 3-5).

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-25

1 March 1949

To: All Ships and Stations

Subj: NavMed-P (Report of Surgical Operations): Reduction of Submission Dates.

Ref: (a) Par. 5113.1, MMD

1. NavMed-P (Report of Surgical Operations) has been required quarterly from all medical activities ashore and from hospital ships, and annually from all other ships. It has been determined that the submission of this report on an annual basis by all ships and stations will adequately meet the needs of the Service.

2. Hereafter NavMed-P (Report of Surgical Operations) shall be prepared and submitted annually by all ships and stations, including hospitals. The report for calendar year 1949 will be the first due under the changed instructions.

3. An advance change in reference (a) will be promulgated to all holders of the Manual of the Medical Department.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-26

1 March 1949

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-10, MMD

Ref: (a) BuMed Circular Letter No. 47-138 of 9 Oct 1947 which enclosed the changes in the Manual of the Medical Department deemed necessary to effectuate the provisions of Public Law 284, 79th Congress, 1st Session.

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change is effective immediately and supersedes the advance changes which were promulgated by reference (a). The distribution of reference (a) and enclosure thereto was limited to one copy to each ship and station having medical or dental officers aboard, and to all dental officers.

2. This Advance Change shall be recorded on the "Record of Changes" page in the Manual. --BuMed. C. A. Swanson

Note: This letter together with the enclosure which consists of 60 pages will be distributed by BuMed as soon as it is received from the printer.

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BUMED CIRCULAR LETTER 49-27

2 March 1949

To: All Activities Under Management Control of the Bureau of Medicine and Surgery

Subj: Procedure for Accomplishment of Work Projects Under the Specific Work Request Authorization; Modification of.

Ref: (a) BuMed Circular Letter No. 48-145

1. Change wording in the first sentence of paragraph 2 of reference (a) from "via the Commandant" to read "information copy to be furnished to the Commandant."

2. Delete the line "Via: (1) Commandant, _____ Naval District" at the top of Enclosure 1 of reference (a); add at the bottom of page copy distribution "CC: Commandant _____ Naval District." --BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-28 Joint Letter 3 March 1949

To: All Ships and Stations

Subj: Cancellation of Certain Joint BuPers-BuMed Letters

In this letter from the Chiefs of BuPers and BuMed, the following joint letters are cancelled:

Navy Department Bulletin No.BuMed Circular Letter No.

44-321
44-703
44-942
44-1238
45-210
45-394
45-1091
45-1216
45-1887
46-2200

44-38
44-105
44-144
44-195
45-56
45-91
45-208
45-228
45-284
46-171

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